Constraint-induced movement therapy and massed practice.

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published in
Stroke
2000

document version
Publisher's PDF, also known as Version of record

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Stroke Association
A Division of American Heart Association

Supplement to the AHA Guidelines for the Management of Transient Ischemic Attacks • Response to Dr Chaturvedi:

Seemant Chaturvedi

Stroke 2000, 31:983-991
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

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Supplement to the AHA Guidelines for the Management of Transient Ischemic Attacks

To the Editor:

I read with interest the recent supplement to the guidelines on management of patients with transient ischemic attacks.[1] However, with regard to carotid endarterectomy (CE), I was disappointed that Albers et al made no attempt to interpret the clinical trial results in the context of real-world surgical performance.

For example, in the updated section on CE for 50% to 69% symptomatic stenosis, the authors state that symptomatic patients with 50% to 69% benefit from surgery and that these patients should be considered for CE. However, should clinicians conclude that because patients in the surgical arm of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) had a marginal statistically significant benefit ($P=0.045$) that this result is clinically meaningful and that this can be routinely achieved in clinical practice?

One must keep in mind that the benefit of surgery in the 50% to 69% group was very modest. For the important clinical outcome of disabling, ipsilateral stroke, the absolute difference between the medical and surgical groups was only 4.4% at 5 years, or less than 1% per year.[2] This modest result was achieved in the ideal setting of low-risk patients being operated on by surgeons screened for their excellence. In NASCET as a whole, the perioperative mortality was 1.1% and the stroke and death rate was 6.5%.

In terms of the real world, Wennberg et al[3] analyzed CE results in over 100 000 Medicare beneficiaries in 1992–1993 and found the perioperative mortality at an average volume hospital to be 1.9%. This was in a mixed symptomatic/asymptomatic cohort. Had the analysis been restricted to symptomatic patients only, the perioperative mortality would likely have been even higher.

With regard to other recent studies, Hartmann et al[4] studied symptomatic patients over a two year period at their hospital and the stroke/death rate was 11.1%. In the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), the rate of *disabling* stroke and death in the CE group was 5.9%, almost 3 times as high as the NASCET figure (M. Brown, personal communication, 1999).

With these considerations, I think that the extremely modest benefit seen in the high-moderate NASCET group is not generalizable and that these patients will not benefit from CE in the real world. The comments of Wennberg et al[3] on the utilization of CE should be heeded when these authors stated that "the caution called for by those advocating restraint is warranted."

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To the Editor:

I must respectfully disagree with the recent AHA Scientific Statement on the management of transient ischemic attacks.[1]

First, the inclusion of the combination antiplatelet agent extended release dipyridamole and aspirin (ERDP/ASA) as a "recommended therapy" is premature. The current data are insufficient to definitively establish that ERDP/ASA offers anything in addition to aspirin alone. Although the results of the ESPS-2 trial[2] of ERDP/ASA are encouraging and generate great optimism for this and other combination strategies, serious questions remain. The ESPS-2 results are highly inconsistent with previous data on 5317 patients treated with the combination.[3] Although a heterogeneous set of trials, these data were sufficient to all but abandon use of dipyridamole in the 1980s. Further, the high rate of subject dropout,[2] the lack of any benefit in vascular death despite the stunning benefit in stroke,[2] the 50-mg dose of ASA,[2,4] and the scientific misconduct[5] discovered in the trial collectively make ESPS-2 inadequate to certify ERDP/ASA as an established therapy by the AHA or any other body.[6] Any new scientific finding that is a large departure from previous data or theory requires independent conformation. Such is true of ERDP/ASA.

Second, a variety of commonly used antithrombotic strategies deserve mention with ERDP/ASA as potentially useful, if unproven, alternatives. This includes the use of clopidogrel or ticlopidine with aspirin,[7–9] a well-accepted standard for poststenting prophylaxis. For some warfarin patients, the addition of any antiplatelet agent can help also.[10,11] Further, for those who are impressed with the dramatic ESPS-2 results of ERDP/ASA, comparable efficacy was observed in the ESPS-1 trial using the inexpensive (and currently available) combination of aspirin (325 mg) and regular dipyridamole (75 mg) 3 times a day.[12] Time and more data will tell if any of these combinations, ERDP/ASA included, can be recommended for general use.

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Response to Dr Chaturvedi:

We thank Dr Chaturvedi for his comments regarding the carotid endarterectomy recommendations in the recently published American Heart Association Guidelines for the Management of Transient Ischemic Attacks. We agree that the efficacy of therapies in the community setting, medical or surgical, may differ from the results obtained in carefully controlled clinically trials. Application of clinical trial results to clinical practice is always problematic and requires clinical judgement. We also agree that surgical morbidity and mortality rates may be higher in the "real world" than those achieved in the North American Symptomatic Carotid Endarterectomy Trial (NASCET). However, the stroke and death rate is also likely to be higher in medically managed patients in a routine practice setting due to variations in the management of comorbid risk factors, decreased emphasis on medical compliance, and less frequent systematic follow-up. In addition, patients selected for participation in clinical trials frequently have relatively favorable outcomes in both active treatment and control groups. Therefore, we do not think it is valid to compare the surgical morbidity and mortality rates in populations such as Medicare beneficiaries with the rates observed in a clinical trial. It is also noteworthy that the NASCET trial enrolled patients with moderate carotid stenosis at 106 diverse clinical sites; therefore, the complication rates reported do exist in the "real world."

Our evidence-based guidelines rely heavily on scientific data from randomized clinical trials. The NASCET and European Carotid Surgery Trial (ECST) provide the highest quality data regarding the risks and benefits of carotid endarterectomy for patients with moderate symptomatic stenosis. The guidelines state that carotid endarterectomy should be "considered" for patients with a recent transient ischemic attack or minor stroke with ipsilateral carotid stenosis of 50% to 69%, but that "the absolute benefit of surgery is relatively small for these patients." The degree of benefit "is highly dependent on surgical risk" and "consideration should be given to clinical features that influence stroke risk and surgical morbidity." These features should include the overall health and gender of the patient, the nature of the neurological symptoms, the degree of stenosis, and the availability of a surgical team with a demonstrated low perioperative morbidity and mortality rate.

Response to Dr Hughes:

We appreciate the opportunity to respond to Dr Hughes. After carefully considering his concerns, we do not believe any modifications of the American Heart Association recommendations[1] are justified. A balanced review of all available data regarding the efficacy of the combination of aspirin/dipyridamole was recently published.[2] When all studies performed in cerebrovascular patients are considered, a substantial and statistically significant benefit of aspirin/dipyridamole over aspirin therapy alone for stroke prevention was detected. The most compelling data supporting the benefits of this combination come from the second European Stroke Prevention Study (ESPS-2) trial that evaluated an extended-release form of dipyridamole (400 mg/d) in combination with aspirin (50 mg/d).[3] As discussed in detail in our report,[1] there is no evidence that the 50-mg dose of aspirin is any less effective for stroke prevention than higher doses, and the aspirin dose recommended by the Food and Drug Administration for stroke prevention is 50 to 325 mg/d. The "scientific misconduct" referred to by Dr Hughes in the ESPS-2 trial reflects a single fraudulent investigator who was identified prior to study completion. The data supplied by this investigator were removed prior to unblinding and analyzing the ESPS-2 data and did not influence the results of study. The dropout rate in the ESPS-2 study did not differ from many similar stroke prevention trials. In addition, a high dropout rate typically dilutes, rather than accentuates, the benefits of an effective agent. The failure of ESPS-2 to demonstrate a reduction in vascular death is also not unique to the aspirin/extended-release dipyridamole combination; neither ticlopidine, clopidogrel, nor any single trial of aspirin therapy has demonstrated a significant reduction in vascular death in patients with cerebrovascular disease.

The American Heart Association is not the first group to recognize the aspirin/extended-release dipyridamole combination as a safe and effective therapy for stroke prevention—this combination was recently approved by the Food and Drug Administration. Other combinations of antiplatelet agents or anticoagulants have not been adequately tested in stroke or transient ischemic attack patients. Therefore, their safety and efficacy are not established.

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Which Targets Are Relevant for Therapy of Acute Ischemic Stroke?

To the Editor:

The report by Heiss et al[1] describing ranges of cerebral blood flow (CBF) decline in 10 patients studied within 3 hours of

stroke onset using the PET technique of intravenous $[^{15}O]H_2O$ injection was intended by the authors to spark discussion. Characterizing the ischemic region into segments that are severely hypoperfused, the ischemic core, moderately hypoperfused, the ischemic penumbra, and minimally hypoperfused or normal will likely provide important information to guide therapeutic options and to determine if any acute treatment at all should be used.[2,3] The data presented by Heiss et al imply that most of the ischemic territory in the patients studied were critically hypoperfused, ie, with CBF levels below 12 mL/100 g per minute, while the penumbral and "sufficiently perfused" components were small, accounting for on average only 18% and 12% of the finally infarcted volume, respectively. The authors suggest that such critically hypoperfused ischemic tissue becomes irreversibly injured rapidly and that "only fast and effective reperfusion strategies" can be potentially useful. The implications suggested by the authors are far reaching, as they imply that only very early (1 to 2 hours) thrombolysis will save the bulk of the at-risk tissue, while the remainder, made up of the penumbra and the sufficiently perfused tissue, may be salvageable by neuroprotective and agents directed against delayed neuronal death (such as anti-inflammatory and antiapoptosis agents), respectively. However, according to the authors, the fact that only small amounts of these latter two tissue subtypes are to be found explains the failure or only marginal efficacy of clinical trials of such pharmacological agents, so that it will be necessary to combine them with early thrombolysis to demonstrate their beneficial effects. These conclusions are provocative and intriguing but differ from prior PET studies using more conventional techniques to measure CBF (and also assessing $CMRO_2$ and the OEF), which have not demonstrated that the critically hypoperfused region is as extensive as the data provided by $[^{15}O]H_2O$ technique, although these prior PET studies were not as hyperacute as the current study.[4–6] This observation is also discrepant with several recent diffusion-perfusion MRI studies that show approximately 70% of stroke patients studied within 6 hours of onset have substantially greater perfusion than diffusion ischemic lesion volumes.[7,8] Diffusion abnormalities likely represent ischemic regions with very low CBF levels. If the patients studied by Heiss et al underwent concurrent diffusion-perfusion MRI, it would be expected that most of the patients would have had diffusion lesions approximating the perfusion lesions. An interesting area for a future study would, therefore, be to perform PET and diffusion-perfusion MRI studies in a group of acute ischemic stroke patients in whom the two studies could be obtained with a close temporal relationship.

The identification of the degree of hypoperfusion with the $[^{15}O]H_2O$ is critically dependent on the accuracy of the method and its interpretation. Does the $[^{15}O]H_2O$ method accurately characterize CBF decline? In theory, the answer is yes. However, because of the use of rtPA, the authors could not apply a fully quantitative method, which implies arterial catheterization. So instead they used a semiquantitative version of the method, in which the CBF is estimated from the side-to-side asymmetry in ^{15}O count-rates on the scans. However, the one paper cited to support this approach is in a nonreferenced source, and further documentation is critical.

In their article, Heiss et al propose what is effectively a novel 3-compartment model of ischemic tissue that comprises (1) a critically hypoperfused component (with CBF $<$12 mL/100 g per minute), which inevitably undergoes necrosis if not rapidly reperfused; (2) a penumbral component (with CBF in the 12 to 18 mL/100 g per minute range), which may spontaneously survive and could be salvageable by neuroprotective agents (and perhaps also by thrombolysis); and (3) a sufficiently perfused component (with CBF $>$18 mL/100 g per minute), which may, however, suffer delayed neuronal death and thus be incorporated in the final infarct. This is an interesting model that the authors propose to explain the results of therapeutic trials in humans, but they do not offer evidence to support its validity. Based on the classic monkey studies of Symon, Astrup and coworkers, and Jones and colleagues of the dynamic penumbra model, most authors consider also 3 compartments but their operational definitions are different, with (1) the core of severely hypoperfused (and hypometabolic) tissue representing the irreversibly damaged tissue at any particular point in time; (2) the penumbra representing all the tissue that can be saved from infarction (taken here to represent pannecrosis, but disregarding selective neuronal death, which is a very marginal occurrence in focal human stroke); and (3) the mildly hypoperfused ("oligemic") tissue, which is not normally at risk of infarction unless some secondary event occurs (such as a fall in systemic blood pressure or severe brain swelling).[9–12] In a paper published in 1998, Heiss et al documented that early thrombolysis ($<$3 hours) was able to entirely salvage the critically hypoperfused compartment ($<$12 mL) in many patients, which would perfectly fit with the classic findings in the monkey that led to the concept of the penumbra.[13] Quantitative PET studies also support this classic model and have allowed determination of validated, probabilistic CBF thresholds during the initial 5- to 18-hours interval after stroke, with CBF $<\approx$8, $\approx$8–17, and $>$17 mL/100 g per minute, for the core, the penumbra and the oligemic tissue, respectively, according to a voxel-based mapping approach in which both gray and white matters are considered.[14,15] Heiss et al use for the core a CBF threshold value of 12 mL, but this value is from early, low-resolution PET studies in which patients were rarely scanned before 24 hours after stroke; moreover, it was calculated from large gray matter ROIs, so that to apply it at the voxel level is questionable, or at least would need to be validated.[16,17] If a threshold for irreversible damage is assumed, it would most likely be much lower than 12 mL, probably around 5 mL or so in the first 3 hours of stroke, which means that the "core" of Heiss et al likely includes both already irreversibly damaged and still-salvageable "at-risk" tissue. Conversely, both their "penumbra" and "sufficiently perfused" tissue are at risk of frank infarction and thus would be incorporated within the penumbra with the classic model. Although it is difficult to strictly compare the findings of Heiss et al with those of Marchal et al, as the individual patient data are not presented in the former, the discrepancies seem more apparent than real, if one takes into account these differences in the models.[6] Thus, in the Heiss article, the extreme percentages of final infarct volumes for the combined penumbra and sufficiently perfused compartments are 8.4% and 63%, consistent with the data of Marchal et al, who reported that the penumbra occupied 10% to 52% of the final infarct (mean 32%) with PET scanning done 5 to 16 hours after onset.

The authors suggest only rapid and effective restoration of blood flow could salvage the large amount of critically hypoperfused ischemic tissue identified by the $[^{15}O]H_2O$ CBF method. Although it remains unknown how long such critically hypoperfused tissue will require to evolve, it is likely not to be very long to permit successful lysis. Since most patients who receive intravenous tPA in the community do so between 2 and 3 hours after stroke onset and yet still derive some benefit, it is unlikely that reperfusion induced by tPA is salvaging only critically hypoperfused tissue to provide clinical improvement. Additionally, in the recently completed PROACT-II study,[18,19] intraarterial thrombolysis initiated with a median time to treat of 5.2 hours demonstrated clinical improvement associated with successful reperfusion 2 hours after therapy was begun in 67% of treated patients. In these patients with angiographically documented, proximal middle cerebral artery occlusions, it is difficult to conjecture that large volumes of critically hypoperfused ischemic tissue could remain potentially salvageable for such an extended time period. We presume that the likely target for both

thrombolytic and neuroprotective therapies for acute ischemic stroke is not likely to be critically hypoperfused ischemic tissue, but instead moderately hypoperfused regions, ie, the ischemic penumbra. It is therefore necessary to have accurate, reliable, and validated imaging methods available to assess blood flow disturbances and the tissue consequences induced by these disturbances to characterize how the ischemic tissue evolves and responds to therapeutic interventions. However, this goal will require the use of both validated methods for CBF assessment and validated pathophysiological models of brain ischemic derangements.

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Response

It is generally accepted that ischemic stroke in evolution is a highly dynamic process involving numerous independent factors and dependent variables. However, in particular the concept of the ischemic penumbra is rather controversial, as can be seen from the various notions provided in the letter of Drs Baron and Fisher. The study described in our contribution was not intended to consolidate those discrepant views. Therefore, out of the many blood flow compartments in the ischemic hemisphere, we focused only on those 3 constituting the ultimate infarct, while regions not undergoing infarction were intentionally left unanalyzed because their fate may have been largely determined by various therapeutic efforts. Therefore, arguments pertaining to the total penumbral zone, including both salvaged and eventually infarcted tissue, are futile, since we had no intention of contradicting observations of widespread severe ischemia that does not necessarily turn into infarction (as indicated, for example, by larger lesions in perfusion compared with diffusion-weighted MRI scans[1,2] and by eventually salvaged, mixed gray/white matter regions exhibiting very low blood flow, even at the postacute stage).[3]

We appreciate the enthusiasm of Drs Baron and Fisher in taking up the discussion we wanted to spark. However, in our view, time would appear to have come to argue about real data rather than concepts. Therefore, what is needed is confirmation or rejection of our findings in appropriate neuroimaging studies performed very early in the evolution of ischemic stroke, ie., at a time when blood flow reveals more of its factorial and not so much of its dependent nature that readily prevails at later points in time, as exemplified by the studies of Furlan et al,[4] in which the PET studies were performed 5 to 18 hours after onset of symptoms.

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1. Baird AE, Warach S. Magnetic resonance imaging of acute stroke. *J Cereb Blood Flow Metab*. 1998;18:583–609.
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Constraint-Induced Movement Therapy and Massed Practice

To the Editor:

Van der Lee and coworkers [1] reported that Constraint-Induced Movement (CI) therapy, compared with bimanual neurodevelopmental treatment (NDT), results in clinically insignificant improvements in the function of the more-impaired arm of persons with chronic stroke. This small effect stands in contrast to the very large improvements in real-world arm use obtained with CI therapy in 3 published studies[2–4] (effect sizes 1.9 to 2.8, Motor Activity Log (MAL);[2,5] large effect size 0.8),[6] an as-yet-

unpublished placebo-controlled study from our laboratory (effect size 2.5, MAL),[7,8] 2 conference presentations,[9,10] and pilot studies from 6 laboratories involved in a national clinical trial of CI therapy with patients with subacute stroke (E. Taub, S. Wolf, C. Winstein, C. Giuliani, D. Good, K. Light, C. Kulkulka, D. Nichols, unpublished data, 1998). Van der Lee et al did not obtain a large treatment effect with their experimental group because the intensity of the therapy provided was inadequate and the subjects selected did not have a large enough deficit before treatment to show substantial benefits from therapy. In addition, we argue that the CI therapy group did not show significantly greater improvement than the bimanual NDT group because this group does not present an appropriate comparison.

In this laboratory, primary attention in CI therapy administration is given to training patients on a massed practice basis.[2,7,8] Patients perform repetitive, behaviorally relevant arm movements with short intertrial and intertask rest periods for 6 to 7 hours daily for at least 2 consecutive weeks. Supervision is provided by a therapist on a continuous, one-on-one basis to ensure intensive practice.[11,12] Van der Lee et al[1] indicate that their experimental patients were treated in groups of 4 by 1 or 2 therapists and that tasks included housekeeping activities, handicrafts, and games. It is unlikely that this treatment format provided patients with adequately intensive practice. When van der Lee and a coauthor visited our laboratory for a week, they described their intended procedure in detail as the performance of hobby-type activities and some ADLs in a relaxed atmosphere without any systematic attempt to get patients to use the more-affected extremity intensively. The actual conduct of the therapy in this fashion was confirmed in a later letter from van der Lee. Before the investigators left this facility, they were strongly advised by 2 senior staff members (J. Crago, MSPT, and S. DeLuca, MA) that what they were planning to do would not work well because it was not sufficiently intense. Their protocol appeared so diffuse that they were told that it would test the *minimum intensity* of practice needed to produce a clinically meaningful effect.

The upper cutoff for experiment intake in our laboratory is a score of 2.5 (less than half as much use of the more-impaired extremity as before the stroke) on the Amount of Use (AOU) scale (range 0 to 5) of the Motor Activity Log (MAL), a semistructured interview of extremity use in the life situation.[2,5] This cutoff is used because the brain injuries of stroke patients impose an upper physiological limit on the amount of improvement that can be produced (a score of 4 on the AOU scale represents "almost normal use"). Furthermore, patients with scores >2.5 do not suffer importantly from "learned nonuse," which is defined as diminished extremity use in the real-world setting relative to ability as measured by a laboratory motor test. Learned nonuse is the target of CI therapy. The mean pretreatment score of experimental subjects in the study of van der Lee et al[1] is 2.2 (SD=1.0), which is significantly greater than the scores (mean=1.1, SD=0.7, n=40) of patients in our experiments ($P<0.001$). The high score indicates that (1) a large minority of patients in the experimental group were too high functioning to have been included in any of the studies cited in the first paragraph and (2) there was little room for treatment-induced improvement in extremity use in the experimental group. In addition, the experimental subjects were higher functioning than their reference subjects on most measures, particularly the MAL, before treatment, thus decreasing the opportunity for improvement relative to the reference group.

In using a reference group given bimanual training based on NDT for 6 hours per day, van der Lee et al ignore our reports that conventional physical therapy, when administered in massed practice fashion, produces an effect that is as good as treatment involving training of the more-affected extremity and restraint of the less-affected extremity.[5,7,8,13] These data, in combination with other findings,[5,7,8,13] have identified the effective therapeutic factor in CI therapy as being the massing or concentration of practice, *however* achieved. It is primarily this factor that is thought to give rise to the massive increase in use-dependent cortical reorganization[14] and other large changes in brain activity[9,15,16] that appear to be the basis of the long-term changes in motor function reported by us.[2–4,8,12] In this light, the (small) treatment effect for the bimanual NDT reference group is to be expected. There are no articles evaluating NDT on nearly as concentrated a basis as employed by van der Lee et al; in effect, they had 2 experimental groups receiving what could be considered 2 different forms of attenuated CI therapy.

Van der Lee et al[1] also criticize the MAL on the grounds that it is a subjective measure and has no established validity. Although the MAL relies on self-report, it is a psychometrically robust instrument. The MAL is stable over a 2-week waiting period[3] and over a 2-week placebo treatment period,[7,8,13] and it has (1) high internal consistency (Cronbach's $\alpha=0.88$ to 0.95), (2) high interrater reliability (patient compared with primary caregiver, intraclass correlation type [3,1][17] =0.90),[5] and (3) high test-retest reliability ($r=0.94$, $P<0.01$). Evidence of validity includes the 0.90 correlation between patient and caregiver reports, a perfect correlation with an observational measure of arm use (Actual Amount of Use Test),[5,7] and a strong association between gains on the MAL and brain reorganization.[9,14–16]

The research from this laboratory was supported by grants B93–629AP and B95–975R from the Rehabilitation Research and Development Service, US Department of Veterans Affairs, and grant HD 34273 from the National Institutes of Health.

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Response

We agree with Drs Taub and Uswatte that the results of the single-blind, randomized, controlled trial we published[1] seem to contradict the results of the studies published by Taub et al,[2] Miltner et al,[3] and Kunkel et al.[4] There are, however, important methodological differences between the studies mentioned by Taub and Uswatte and our study, and we consider this to be the most probable explanation of the apparent differences in results. Obviously, we are unable to comment on the unpublished studies mentioned by Taub and Uswatte. The studies presented by Kunkel et al and Miltner et al are uncontrolled case-series studies. Uncontrolled studies can be misleading and will almost always report grossly overestimated treatment effects.[5] There are 2 principal methodological differences between the randomized trial published by Taub et al[2] and our study: the number of patients (9 versus 66, respectively) and the intervention in the control group ("attention-control" versus intensive bimanual treatment, respectively). The contrast between the so-called "attention-control" intervention and the experimental intervention applied by Taub et al comprises not only specific but obviously also nonspecific aspects. In our opinion, this is illustrated by Figure 3 included in the article of Taub et al, in which half of the effect of the treatment in the experimental group appears to take place on day 1 of the treatment. In their letter, Taub and Uswatte mention 3 tentative explanations as to why we did not find a greater treatment effect: inadequate intensity of therapy, inadequate selection of patients, and inadequate contrast between the experimental and the control interventions. Furthermore, they contradict our criticism of the Motor Activity Log (MAL). We will reply to each of these items separately.

Intensity of treatment. We are somewhat puzzled by this criticism from Taub and Uswatte, because it is contradicted by their later statement that the improvement in our reference group was the result of the high intensity of treatment ("concentrated schedule of delivery"). Indeed, the intensity of treatment was high in both the experimental and the reference groups in our trial.

Selection of patients. It is true that we used a different outcome measure to the MAL to establish the upper cutoff for inclusion in our study, ie, the Action Research Arm (ARA) test, which was a primary outcome measure in our study. It is, indeed, conceivable that at higher pretreatment levels the MAL suffers from a ceiling effect. Nevertheless, we did find differential effects on the MAL, but these did not last.[1] To investigate the assumption that a more rigourous selection of patients would have yielded greater treatment effects, we reanalysed the subgroup of patients in our trial whose pretreatment MAL Amount Of Use (AOU) score was <2.5, as suggested by Taub and Uswatte. Somewhat to our surprise, however, we did not find a statistically significant difference in effectiveness in this subgroup (n=43), the mean difference in improvement on the MAL AOU scale between groups being 0.32 points (95% CI −0.10 to 0.75). This means that it could also be argued that higher-scoring patients are more liable to improve than patients with less residual arm function. On the ARA test, the difference in improvement between groups was significant in this subgroup, ie, 3.4 points (95% CI 1.3 to 5.6) and not notably different from the effect in the entire study population, ie, 3.0 points (95% CI 1.3 to 4.8).

Contrast between the experimental and the control interventions. We agree that the contrast between the experimental and the control interventions in our trial was relatively small. The main objective of our study was to investigate the *specific* effect of forced use, ie, the immobilization of the unaffected arm. We tried to make the control treatment equally intensive, to adjust for the nonspecific effects of treatment intensity. It is, indeed, conceivable that the intensity of the treatment is the most effective aspect of the treatment, designated as constraint-induced movement therapy, but this has not yet been shown in publications of well-designed studies in peer-reviewed journals. As we stated in the discussion paragraph of our article, the improvement in the control group may very well have been the result of the intensive physical and occupational therapy, which was equally intensive in the experimental group. The use of a splint and sling to immobilize the unaffected arm is very unpleasant and potentially dangerous. If a similar effect can be obtained by intensive bimanual treatment, this is of crucial importance for clinical practice. This would imply that the term "constraint-induced" can be replaced by "intensive." The effectiveness of enhanced intensity of treatment for stroke patients has recently been shown by Kwakkel et al.[6]

Validity and reliability of the MAL. The statement that the MAL is stable over a 2-week waiting period is not confirmed by the data presented by Miltner et al.[3] The MAL AOU and Quality Of Movement (QOM) data differ significantly between first contact and baseline (AOU, $P=0.023$; QOM, $P=0.047$), and between baseline and pretreatment (AOU, $P=0.006$; QOM, $P=0.022$), respectively (Wilcoxon signed rank test). In 2 of the articles claimed to confirm the stability of the MAL over a 6-week placebo treatment and follow-up period, no data were presented.[7,8] More importantly, the possibility that reported changes on the MAL are the result of a Hawthorne effect remains unchallenged.

We hope that the readers, when weighing up the arguments in the letter from Taub and Uswatte and our reply to their criticism, will not forget that to date only 2 randomized controlled trials[1,2] on the question at issue have been published, of which ours[1] is by far the largest. We therefore wish to reemphasize the importance of our findings. We hope that the positive aspect of our conclusion, that the effect of forced use was clinically relevant in subgroups of patients with sensory disorders and hemineglect, will be a challenging starting point for future research.

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Effects of Statins on Ischemic Stroke: Neuroprotection and/or Triggering of Apoptotic Damage?

To the Editor:

In their recent review, Drs Vaughan and Delanty[1] have proposed that statins, which inhibit the activity of a key enzyme in the biosynthesis of cholesterol and isoprenoids (β-hydroxy-methyl-β-glutaryl coenzyme A reductase), may represent a clinically important class of drugs in human neuroprotection. This proposal is first based on the results of clinical trials and meta-analysis indicating that statin therapy lowers stroke risk by ≈30%. In addition, several experimental results reviewed by these authors suggest that statins may act by making the brain parenchyma cells "more resistant to the effect of ischemia." Indeed, statins appear to exert anti-inflammatory and antioxidative properties and to modulate the effects of various cytokines.

Despite the bundle of evidence toward a beneficial action of statin therapy, it appears to me that some of the effects of statins that might be less attractive have perhaps been overlooked. Indeed, there have been in the last few years several reports showing that inhibition of cholesterol biosynthesis by statins induces apoptosis in various cellular models, including cortical neurons in culture,[2] human and rat glioma cells,[3–5] as well as PC 12 cells.[6,7] Similarly, we have shown in PC 12 cells that mevastatin treatment first induces an aborted differentiation followed by a programmed cell death (D. Duval, PhD, unpublished data, 1999). Although the mechanisms leading to glioma and neuronal cell damage are not fully understood, it generally appears that statins act by inhibiting the isoprenoid pathway and blocking the isoprenylation of protein(s) involved in the control of cell proliferation and survival.[8–10] It has been shown, for example, that statin treatment induces a cytoplasmic accumulation of Rho A in renal mesangial cells[11] or p21 WAF1 induction in vascular smooth muscle cells.[8]

Additional experiments are clearly needed to determine whether or not such an apoptotic effect of statins may occur in the brain under either physiological and/or pathological situations such as trauma and focal ischemia. Michikawa and Yanagisawa[2] have described that cultures of cortical neurons become more susceptible to the toxic action of apolipoprotein E4 under conditions of de novo suppressed cholesterol biosynthesis. Nevertheless, given the possibility that statins may exert deleterious effects on brain cells, it is probably prematurate to state that inhibitors of cholesterol biosynthesis represent potential neuroprotective agents, and caution should thus be required before undertaking larger clinical trials in humans.

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Response

We thank Dr Duval for his interest in our article[1] and appreciate his concern about potential deleterious effects of statins within the nervous system, particularly his concern about the possible induction by statins of apoptosis within the brain. We agree that any adverse effects of statins should be thoroughly investigated. Indeed, we drew attention to the possible inhibition of coenzyme Q_{10} biosynthesis by lovastatin as one example. We have a number of additional comments in reply to Dr Duval.

First, our article was essentially hypothesis generating rather than a statement of fact. The unequivocal demonstration of neuroprotection with statins in humans must await further study, especially employing large randomized trials in specific situations, eg, after acute stroke. In addition, not all statins may exert neuroprotection, and there may be differential effects within this class.[2]

Second, our hypothesis was based on published data from studies of various types, which included large, randomized, placebo-controlled trials in patients with or at risk of vascular disease; observational studies using surrogate end points of endothelial function in humans; relevant animal studies, including important studies measuring cerebral blood flow in normocholesterolemic mice; as well as studies using in vitro models. On the other hand, Dr Duval's concerns arise from studies exclusively carried out in vitro utilizing cultured glial cells and neurons. Although of interest, these studies may be of least relevance when applied to clinical therapeutics and thus need further confirmation in other models. These in

vitro studies are also apt to be compounded by the specific cell lines used and drug concentrations. In addition, some of these studies have used transformed cell lines, such as human malignant glioma cells and promyelocytic cells, and therefore the data may not be applicable to healthy but at risk tissue, such as that within the ischemic penumbra in acute stroke. In one study quoted by Dr Duval, lovastatin was shown to induce apoptosis in human malignant glioma cells, leading the authors of the study to speculate that such an approach with statins "merit further investigation as potential therapeutic agents for the treatment of malignant gliomas."[3] Furthermore, if statins induce apoptosis in both nonmalignant "healthy" glia as well as in malignant glial cells, it is not intuitively obvious that this would necessarily be deleterious; in some circumstances, the inhibition of active gliosis[4] could be beneficial and ameliorate brain dysfunction. Again, these complex, interesting, and highly relevant questions can be optimally addressed only in human studies using clinical outcome data, perhaps in conjunction with novel noninvasive markers of neuronal function such as magnetic resonance spectroscopy.

Finally, Dr Duval's concerns about possible adverse effects of statins are immediately relevant to the large numbers of patients worldwide currently taking these drugs. Patients with hypercholesterolemia and those with coronary artery disease are at significant risk for concomitant disease within the cerebral vasculature, and it is likely that a large number of patients with established cerebrovascular disease are already being treated with various agents of the statin class. We disagree that clinical trials should be inhibited on the basis of the studies cited by Dr Duval. There is no evidence in vivo of neurological decline in patients receiving statin therapy, and the suggestion that these compounds may be proapoptotic in the normal or ischemic brain is pure speculation. The points raised by Dr Duval underscore the need for prospective, randomized, placebo-controlled trials to explore the efficacy of statin therapy in human neuroprotection. Ongoing studies such as the The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study[5] will help clarify their role in human cerebrovascular disease.

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Frequent Polymorphism of the Human Methylenetetrahydrofolate Reductase

To the Editor:

In the recent article by Bova et al,[1] the authors describe a significant association of the "alanine/valine (A/V) polymorphism at codon 677 of the 5, 10 methylenetetrahydrofolate reductase (MTHFR) gene." This polymorphisms was abbreviated in the title with A677V. There have been multiple studies on the impact of this so-called thermolabile variant of MTHFR and moderate hyperhomocysteinemia and/or atherosclerotic vasculopathies. The variant is characterized by a C→T transition of nucleotide 677.[2] Codon 677, which is described by the authors throughout the paper, is not affected. Obviously, the authors mixed up the genetic terms nucleotide position and codon, which may confuse the reader. The common nomenclature of the MTHFR thermolabile variant is C677T, or more accurately according to the Nomenclature Working Group,[3] c.677C→T.

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Response

We thank Mr Linnebank, Mr Homberger, and Dr Koch for pointing out the problematic nomenclature of the thermolabile MTHFR variant. The most accurate description of the mutation studied in our paper is indeed MTHFR 677C-T.

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The A677V MTHFR Allele Is Not Associated With Carotid Atherosclerosis in Octogenarians

To the Editor:

We read with interest the article by Bova et al,[1] published in the October 1999 issue of *Stroke*, on the association of the MTHFR A677V gene allele with carotid atherosclerosis. We have just finished a study aimed to characterize very old people with "vascular successful aging" (VSA), which we define according to the following criteria: (1) age ≥75 years; (2) negative history for cardiovascular disease; (3) absence of clinical symptoms and ultrasonographic/Doppler signs (duplex sonography) of extracoronary (epiaortic, abdominal aortic, iliac, and femoral) atherosclerosis, ie, lack of any focal protrusion ≥1.5 mm; and (4) absence of clinical symptoms and ECG signs of coronary artery disease. These subjects were compared with a control group selected by the following criteria: (1) age ≥75 years and (2) presence of carotid atherosclerosis, ie, a plaque inducing a 30% to 50% stenosis. They may have a positive history for cardiovascular disease, provided that no acute episode occurred in the

3 months before inclusion in the study. A total of 57 subjects, 29 with VSA and 28 with carotid atherosclerosis (AG), were enrolled. The mean age in both groups was >80 years (80.9 and 81.8, respectively). We found several differences between the VSA subjects and controls in plasma and LDL antioxidant levels as well as in LDL oxidation level. Among the possible genetic markers of vascular successful aging, we also determined the A677V MTHFR gene polymorphism by the method of Frosst et al,[2] but we did not find any association with the vascular status. The frequency of the A677V allele was 52% in the VSA group and 39% in the AG group (χ^2=NS), while the frequency of homozygosity was 36% in VSA and 10% in the AG group (χ^2=NS). Genotype frequencies conformed to the Hardy-Weinberg equilibrium. In the study of Bova et al, the subjects were significantly younger than in our study and the control group suffered from mild carotid atherosclerosis. Because atherosclerosis is a progressive disease, subjects with a mild stenosis in adult age, as the control group presented in the study, might develop greater stenosis in late life and therefore might not represent an ideal control for comparison. Moreover, only 19% of the subjects with severe carotid atherosclerosis were homozygous, a condition that has been clearly associated with increased homocysteine levels.[2]

Our results suggest that this polymorphism is not associated with the presence, or with the absence, of moderate to severe carotid atherosclerosis in very advanced age. However, it is possible that the A677V gene polymorphism is associated with atherosclerosis in a younger population as well as in different ethnic groups.

Because the relationship between A677V gene polymorphism and carotid atherosclerosis is still controversial,[3,4] more research must be done in this field before any conclusion can be drawn.

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Response

We thank Zuliani and colleagues for describing their observations on carotid stenosis and the MTHFR 677c-t allele. As these authors note, their patient population was significantly older than the patients in our study and were chosen by somewhat different criteria. In this population the MTHFR 677c-t allele was less common in patients with moderate carotid stenosis than in age-matched patients with no significant cardiovascular disease. Although it is difficult to compare our study with the results of Zuliani et al, the differences between elderly and younger patients seem to be analogous with the well-established association of the APOE ϵ4 allele and Alzheimer's disease. In the case of APOE, the ϵ4 allele is associated with earlier age of onset of disease; due to earlier mortality in Alzheimer's disease, in the population aged >80 years it is no longer more common in Alzheimer patients than in controls.[1,2]

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